DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

PMA P910071

Memorandum

Date NOV 4 1994

From Director, Office of Device Evaluation (HFZ-400)
Center for Devices and Radiological Health (CDRH)

Subject Premarket Approval of Chiron Vision Corporation
Adatomed Silicone Oil OP5000 - ACTION

To The Director, CDRH
ORA _____

ISSUE. Publication of a notice announcing approval of the subject PMA.

FACTS. Tab A contains a FEDERAL REGISTER notice announcing:

(1) a premarket approval order for the above referenced medical device (Tab B); and

(2) the availability of a summary of safety and effectiveness data for the device (Tab C).

RECOMMENDATION. I recommend that the notice be signed and published.

Susan Alpert, Ph.D., M.D.

Attachments
Tab A - Notice
Tab B - Order
Tab C - S & E Summary

DECISION

Approved _____ Disapproved _____ Date _____

Prepared by Everette T. Beers, Ph.D., CDRH, HFZ-460, 10/14/94, 594-2018
Emma J. Knight, M.D., CDRH, HFZ-460, 10/14/94, 594-2018
Debra Y. Lewis, O.D., CDRH, HFZ-460, 10/14/94, 594-2018

DRAFT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

[DOCKET NO. _____]

CHIRON VISION CORPORATION; PREMARKET APPROVAL OF ADATOMED SILICONE OIL OP5000

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its approval of the application by Chiron Vision Corporation, Irvine, CA, for premarket approval, under section 515 of the Federal Food, Drug, and Cosmetic Act (the act), of Adatomed Silicone Oil OP5000. After reviewing the recommendation of the Ophthalmic Devices Panel, FDA's Center for Devices and Radiological Health (CDRH) notified the applicant, by letter on NOV 4 1994, of the approval of the application.

DATE: Petitions for administrative review by (insert date 30 days after date of publication in the FEDERAL REGISTER); Written comments by (insert date 30 days after date of publication in the FEDERAL REGISTER).

ADDRESS: Written requests for copies of the summary of safety and effectiveness data, petitions for administrative review, and comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 1-23, 12420 Parklawn Drive, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Debra Y. Lewis, O.D.
Center for Devices and Radiological Health (HFZ-460)
Food and Drug Administration
9200 Corporate Boulevard
Rockville, MD 20850
301-594-2018.

SUPPLEMENTARY INFORMATION: On March 5, 1992, Chiron Vision Corporation, Irvine, CA 92718-1903, submitted to CDRH an application for premarket approval of Adatomed Silicone Oil OP5000. The device is an intraocular fluid and is indicated for use as a prolonged retinal tamponade in selected cases of complicated retinal detachments.

On October 28, 1993, the Ophthalmic Devices Panel, an FDA advisory panel, reviewed and recommended approval of the application.

On NOV 4 1994, CDRH approved the application by a letter to the applicant from the Director of the Office of Device Evaluation, CDRH.

A summary of the safety and effectiveness data on which CDRH

based its approval is on file in the Dockets Management Branch (address above) and is available from that office upon written request. Requests should be identified with the name of the device and the docket number found in brackets in the heading of this document.

OPPORTUNITY FOR ADMINISTRATIVE REVIEW

Section 515(d)(3) of the act (21 U.S.C. 360e(d)(3)) authorizes any interested person to petition, under section 515(g) of the act (21 U.S.C. 360e(g)), for administrative review of CDRH's decision to approve this application. A petitioner may request either a formal hearing under part 12 (21 CFR part 12) of FDA's administrative practices and regulations or a review of the application and CDRH's action by an independent advisory committee of experts. A petition is to be in the form of a petition for reconsideration under 10.33(b) (21 CFR 10.33(b)). A petitioner shall identify the form of review requested (hearing or independent advisory committee) and shall submit with the petition supporting data and information showing that there is a genuine and substantial issue of material fact for resolution through administrative review. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issue to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

Petitioners may, at any time on or before (insert date 30 days after date of publication in the FEDERAL REGISTER), file with the Dockets Management Branch (address above) two copies of each petition and supporting data and information, identified with the name of the device and the docket number found in brackets in the heading of this document. Received petitions may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. This notice is issued under the Federal Food, Drug, and Cosmetic Act section 520(h), 90 Stat. 554-555, 571 (21 U.S.C. 360e(d), 360j(h)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Director, Center for Devices and Radiological Health (21 CFR 5.53).

Dated:_____.

_____

D. Bruce Burlington, M.D.
Director
Center for Devices and
Radiological Health

CERTIFIED TO BE A TRUE COPY OF THE ORIGINAL

_____

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville MD 20850

NOV - 4 1994

Judy F. Gordon, DVM
Vice President, Scientific Affairs
Chiron Vision Corporation
9342 Jeronimo Road
Irvine, California 92718-1903

RE: P910071
Adatomed Silicone Oil OP5000
Filed: March 5, 1992
Amended: February 21, April 14 and 22, May 14, 18, and 20, and October 9, 1992; January 11, April 22 and 23, July 15, August 25, September 15 and 21, October 13, 14, 21, 25, 27, and 28, November 12, and December 20, 1993; and, March 14, 30, and 31, May 17, and October 19, 1994.

Dear Dr. Gordon:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the Adatomed Silicone Oil OP5000. This device is indicated for use as a prolonged retinal tamponade in selected cases of complicated retinal detachments where other interventions are not appropriate for patient management. Complicated retinal detachments or recurrent retinal detachments occur most commonly in eyes with proliferative vitreoretinopathy (PVR), proliferative diabetic retinopathy (PDR), cytomegalovirus (CMV) retinitis, giant tears, and following perforating injuries. Adatomed Silicone Oil OP5000 is also indicated for primary use in detachments due to Acquired Immune Deficiency Syndrome (AIDS) related CMV retinitis and other viral infections. We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

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In addition to the postapproval reporting requirements discussed in the enclosure, you must submit a draft protocol within 60 days for a postapproval prospective study. This protocol should provide data on 100 patients that document the timing of silicone oil removal and that assess complication rates. Anatomic reattachment and visual acuity outcomes should be the end points studied in relationship to the timing of oil removal. The study should be conducted in patients who have had the device placed in the eye for repair of retinal detachment associated with giant retinal tear (GRT) or proliferative vitreoretinopathy (PVR). The goal is to provide a cohort of patients who can be serially followed until the oil is removed, and to follow the outcome of those patients for six months after oil removal. Only patients in whom visual acuity is hand-motion or better and at least 75% of the retina is reattached one month postoperatively should be enrolled. Further, patients with cytomegalovirus (CMV) retinitis should be excluded, because these patients are also unlikely to undergo silicone oil removal. Patients with traumatic retinal detachments and proliferative diabetic retinopathy also should be excluded, because of the great variation in the status of these eyes. Patients should be enrolled into the study one month after the silicone oil has been placed in the eye.

The study should be divided into two phases. The first phase should begin after the patient has had successful reattachment of the retina with silicone oil and is one month postoperative. This phase will continue with regular follow-up until the oil is removed. The second phase of the study will begin when the oil is removed, and will assess patient outcome after oil is removed. Visual acuity, corneal clarity, lens status, intraocular pressure, gonioscopy and assessment of oil emulsification and retinal attachment should be compared in each patient during the first and second phases of the study.

The postapproval progress reports must be provided annually. A final report is expected 6 months after the completion of the study. Results of the study should be reflected in the labeling (via a supplement to your PMA) when the postapproval study is completed.

Expiration dating for this device has been established and approved at 2 years when stored at room or cool temperature (8°C to 24°C). You should submit a supplement to this PMA containing the updated expiration dating protocol if you intend to extend your approved shelf life.

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the act.

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Everette T. Beers, Ph.D. at (301) 594-2018.

Sincerely yours,

Susan Alpert, Ph.D., M.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

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A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the **addition** of, but **not the replacement** of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgement by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This acknowledgement is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. **This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.**

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant**(s)** involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

(1) Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

(2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

(a) unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

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(b) reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

(1) A mixup of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984, and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to FDA whenever they receive or otherwise became aware of information that reasonably suggests that one of its marketed devices

(1) may have caused or contributed to a death or serious injury or

(2) has malfunctioned and that the device or any other device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for this PMA, you shall submit the appropriate reports required by the MDR Regulation and identified with the PMA reference number to the following office:

Division of Surveillance Systems (HFZ-544)
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Drive, Room 3083
Rockville, Maryland 20850
Telephone (301) 594-2735

Events included in periodic reports to the PMA that have also been reported under the MDR Regulation must be so identified in the periodic report to the PMA to prevent duplicative entry into FDA information systems.

Copies of the MDR Regulation and an FDA publication entitled, "An Overview of the Medical Device Reporting Regulation," are available by written request to the above address or by telephoning (301) 594-2735.

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SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. General Information

A. Device Generic Name: Intraocular Fluid
B. Device Trade Name: Adatomed Silicone Oil OP5000
C. Applicant's Name and Address:

Chiron Vision Corporation
9342 Jeronimo Road
Irvine, CA 92718-1903

D. Investigational Device Exemption (IDE) Numbers:

Chiron: G880198
Others using Adatomed Silicone Oil, e.g.: G880188, G870213, G880014, G880081, G880105, G880110, G880049, G880128, G880152, G880084, G860132, G900003.

E. Date of Panel Recommendation: October 28, 1993
F. Premarket Approval Application (PMA): P910071
Date Filed: December 16, 1991
Date Approved: NOV 4 1994
G. GMP Inspection: August 1, 1994

II. Indications for Use

Adatomed Silicone Oil OP5000 is indicated for use as a prolonged retinal tamponade in selected cases of complicated retinal detachments where other interventions are not appropriate for patient management. Complicated retinal detachments or recurrent retinal detachments occur most commonly in eyes with proliferative vitreoretinopathy (PVR), proliferative diabetic retinopathy (PDR), cytomegalovirus (CMV) retinitis, giant tears, and following perforating injuries. Adatomed Silicone Oil OP5000 is also indicated for primary use in detachments due to Acquired Immune Deficiency Syndrome (AIDS) related CMV retinitis and other viral infections.

III. Device Description

Adatomed Silicone Oil OP5000 is a sterile, highly purified long chain polydimethylsiloxane. It is a clear colorless liquid at room temperature with a viscosity of 5000-5400 centistokes (cst) (nominal 5000 centistokes). Adatomed Silicone Oil OP5000 [α,ω-bis (trimethylsiloxy)- poly(dimethylsiloxane)] is a copolymer, having an average molecular weight of 54,000 ($\pm$ 10%), and is synthesized from dichlorodimethylsilane and chlorotrimethylsilane. The final product contains approximately 99.5 mol% of $(CH_3)_2SiO$ subunits and 0.5 mol % $(CH_3)_3SiO_{0.5}$ subunits. Adatomed Silicone Oil OP5000 has a high surface tension (21 mN/m) and is immiscible with aqueous components. It has the following formula:

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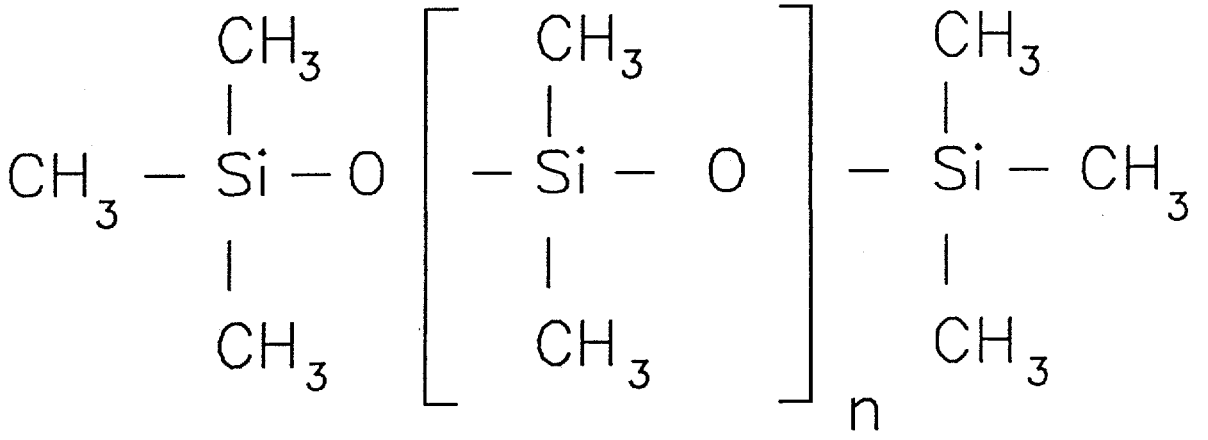

It has a specific gravity (25°C) between 0.96 and 0.98 g/cm^3 and a refractive index (25°C) between 1.403 and 1.405. Low molecular weight siloxanes are $\leq$ 0.0050% (50 ppm) for each detectable cyclic or linear species and $\leq$ 0.02% (200 ppm) for the aggregate of all detectable species. Each 1 mL contains solely polydimethylsiloxane oil in neat form.

Adatomed Silicone oil OP5000 has the following physical and chemical specifications:

Specifications:

Specific gravity (25°C)	0.96-0.98 g/cm^3
Refractive index (25°C)	1.403-1.405
Viscosity (25°C)	5000-5400 cst
Polydispersity (MW/MN)	1- 2.3
Volatility	0-0.1%
Specific resistivity	1-200 X 10^{15} Ohm cm
Low Molecular Weight Siloxanes	$\leq$ 50ppm each; $\leq$ 200ppm aggregate
Surface tension	21 mN/m
Content of -OH end groups	< 100 ppm (wt)
Solubility of air	0.175-0.190 cc/gm

Adatomed Silicone Oil OP5000 is supplied in sterile 10mL and 15mL glass vials.

IV. Contraindications, Precautions, and Adverse Reactions

A. **Contraindications.** As silicone oil can chemically interact with and opacify silicone elastomers, the use of Adatomed Silicone Oil OP5000 is contraindicated in pseudophakic patients with silicone intraocular lenses.

B. **Precautions.**

- Adatomed Silicone Oil OP5000 is supplied in a sterile vial intended for single use only and contains no preservative.

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- Do not resterilize.
- Discard unused portions of Adatomed Silicone Oil OP5000.
- Do not admix oil with any other substances prior to injection.
- Product should be discarded following expiration date.
- The safety and effectiveness of long-term use of Adatomed Silicone Oil OP5000 has not been established.

C. **Adverse Reactions.** The data supporting the rates of occurrence of adverse reactions were derived from the following studies: (1) a study reported in K. Lucke and H. Laqua, *Silicone Oil in the Treatment of Complicated Retinal Detachments*, Springer-Verlag, Berlin, 161 pages, 1990, (299 eyes with Adatomed Silicone Oil OP5000; 236 with complete follow up at 6 months or longer); (2) a U.S.-based multicenter clinical trial (155 subjects); and, (3) independently sponsored investigations of the use of the oil in AIDS related CMV retinitis (205 eyes). The percentages reported below represent the range of occurrence for all of the studies reporting the same adverse reaction. In cases where only one of the studies recorded a particular endpoint, only that percentage, as well as the study from which it was derived, is reported.

1. **Cataract.** Approximately 50-70% of phakic subjects developed a cataract within 12 months of oil instillation. Approximately 33% of phakic AIDS CMV retinitis subjects developed some degree of cataract within an average 4-5 month time frame from oil instillation.

2. **Anterior chamber oil migration.** In 17-20% of treated subjects oil emulsification and/or migration into the anterior chamber was observed. Migration into the anterior chamber occurred in both phakic and aphakic subjects.

3. **Keratopathy.** From 8%-20% of subjects developed keratopathy (0.6%, AIDS study). This complication occurred most frequently in aphakic subjects (18-21%) and in the subjects in whom oil had migrated into the anterior chamber (30%, Lucke study); the keratopathy in these cases was attributed to prolonged physical contact between the corneal endothelium and the silicone oil.

4. **Glaucoma.** Approximately 19-20% (0.6%, AIDS study) of subjects developed a persistent elevation in intraocular pressure (IOP) (> 23-25 mm Hg, depending on study definitions). The neovascular glaucoma rate was about 8% (Lucke). Moderate temporary post-operative increases occurred within the first 3 weeks of treatment. Thereafter, secondary ocular hypertension occurred by several mechanisms. Glaucoma complications occurred in approximately 30% of subjects in which anterior chamber oil was noted (Lucke study). Subjects with proliferative diabetic retinopathy were at highest risk for development of glaucoma following silicone oil instillation into the vitreous space.

5. **Other.** In addition to the complications above, other less commonly occurring reactions reported in Lucke (236 eyes) in greater than 2% of subjects, ranked by frequency of occurrence, included: redetachment, optic nerve atrophy, rubeosis iridis, temporary IOP increase, macular pucker, vitreous hemorrhage, phthisis, traction detachment, and angle block.

The following complications occurred at rates of less than 2%: subretinal strands, retinal rupture, endophthalmitis, subretinal silicone oil, choroidal detachment, aniridia, PVR reproliferation, cystoid macular edema, and enucleation.

V. Alternative Practices and Procedures

Silicone oil is used as a postoperative tamponade following vitreous surgery in cases of complicated retinal detachment either when the eye has failed previous attempts to reattach the retina, or when the condition of the eye or of the patient makes surgery with alternative practices unlikely to succeed.

Conventional retinal surgery for retinal detachments consists of scleral buckle surgery (Custodis 1953, Schepens 1964, and Lincoff et al. 1965), sometimes accompanied by external drainage of subretinal fluid through a sclerotomy, and cryotherapy or laser photocoagulation of the edges of the retinal tears (Meyer-Schwickerath 1959 and Lincoff et al. 1964). These procedures are effective in most cases of primary retinal detachment. Some cases of retinal detachment present with conditions that make scleral buckling surgery less effective such as: posteriorly located retinal breaks, significant scar tissue on the surface or underneath the retina which exerts traction on the retina preventing reattachment, or optical problems which obstruct the view of the retina. In detachments complicated by these conditions, many such eyes can be treated successfully with vitrectomy techniques, during which the retina is repositioned into its normal location by endodrainage of subretinal fluid through holes in the retina during an exchange of the normal intraocular fluid contents for either air, or a long acting gas (Fineberg et al. 1975, Machemer and Laqua 1978, Abrams et al. 1982, and Lucke and Laqua 1990).

Following initially successful retinal detachment surgery, intraocular scar tissue can proliferate to an extent that the scar tissue exerts enough traction on the retinal surface to cause retinal redetachment. This condition is called proliferative vitreoretinopathy (PVR). In order to repair detachments with significant amounts of PVR, the scar tissue must be peeled off of the retina (Machemer and Laqua 1978, Michaels 1981, and Charles 1981). Following this membrane peeling, the retina is repositioned and the vitreous cavity is filled with an agent to act as a tamponade to keep the retina in its normal position while a chorioretinal scar is forming induced by photocoagulation or cryotherapy of the retina surrounding retinal tears. Various gas tamponades are used, such as perfluoropropane and sulfurhexafluoride (Lincoff et al. 1983, and Faulbourn and Bowald 1987). These intraocular gas bubbles gradually decrease in size. As the bubbles decrease in size, it becomes imperative that patients position their heads in order to keep the gas bubble opposed to the areas of the retinal breaks. If the retinal tears are inferior, the patient often must maintain strict face down positioning for extended periods of time.

VI. Dosage and Administration

Adatomed Silicone Oil OP5000 can be used in conjunction with or following standard retinal surgical procedures including scleral buckle surgery, vitrectomy, membrane peeling, and retinotomy or relaxing retinectomy.

Aseptically remove the sterile vial of Adatomed Silicone Oil OP5000 from the peel back pouch onto the sterile tray. Load the oil into a sterile Luer-Lok screw syringe or Luer-Lok syringe adaptable to an automated pump system. Introduction of air bubbles into the oil should be avoided by careful

withdrawal or decanting of the oil into the syringe. The oil can be injected into the vitreous from the syringe via a single-use cannulated infusion line or syringe needle. Subretinal fluid can be drained with a flute needle concurrent with Adatomed Silicone Oil OP5000 infusion. The vitreous space can be filled with the oil to between 80% and 100% while exchanging for fluid or air, taking necessary precautions to avoid high intraocular pressure from developing during the exchange. Because the Adatomed Silicone Oil OP5000 is less dense than the eye's aqueous fluid, a basal iridectomy at the 6 o'clock meridian (Ando iridectomy) is recommended to minimize oil induced pupillary block and early angle-closure glaucoma. At the physician's discretion, it may be desirable to have the patient assume a face-down posture during the first 24 hours following surgery.

The patient should be monitored closely by the physician for development of glaucoma, cataract, and keratopathy complications and be scheduled for follow up reexamination at regular intervals.

It is recommended that Adatomed Silicone Oil OP5000 be removed at an appropriate interval within 1 year following instillation if the retina is stable, attached, and without significant remnants of proliferation. Although there is insufficient clinical evidence to support justification for longer term tamponade, whether or not the oil should be removed in patients at high risk for redetachment or the development of phthisis and shrinkage due to hypotony must be determined individually by the physician. In order to minimize the number of invasive traumatic experiences for patients with AIDS and CMV retinitis at high risk for redetachment and who have a shortened expected lifespan, it may be desirable to avoid silicone oil removal procedures if the patient concurs.

Adatomed Silicone Oil OP5000 can be removed from the posterior chamber by withdrawal with a normal 10 mL syringe and a wide bore 1 mm cannula. By repeated oil-fluid exchange most of the remaining small silicone oil droplets can subsequently be mobilized and removed from the eye. Alternatively, oil may be passively removed by infusion of an appropriate aqueous solution under the oil bubble, while allowing the oil to effuse out of a sclerotomy incision, or a limbal incision in aphakic patients.

As there is a possible correlation between the migration of Adatomed Silicone Oil OP5000 into the anterior chamber and the appearance of corneal changes such as edema, hazing or opacification, Descemet folds, or decompensation, regular monitoring of the patient's corneal status should be performed and early corrective action taken if necessary, including extraction of the oil from the anterior chamber. Large bubbles or droplets of oil in the anterior chamber can be removed manually by syringe. Further standard practice for medical treatment of the keratopathy is recommended.

Temporary pressure increases more than 3 weeks after surgery which either normalize spontaneously or can be corrected by surgical treatment are those in which the Adatomed Silicone Oil OP5000 causes a mechanical blockage of the pupil or inferior iridectomy or causes chamber angle closure by forcing its way anteriorly. In these situations some of the oil may be withdrawn to relieve the mechanical force of the oil interface. Presence of Adatomed Silicone Oil OP5000 droplets in the anterior chamber may also cause a chronic outflow obstruction of the trabecular meshwork. In such situations, elevated intraocular pressure can be managed with anti-glaucoma medication in the majority of outflow obstruction patients.

Adatomed Silicone Oil OP5000 should be stored at cool or room temperature (8° to 20°C).

VII. Marketing History

Adatomed Silicone Oil OP5000 for retinal tamponade has been produced by Adatomed GmbH since 1986 and distributed to all Scandinavian and European countries with the exception of Portugal and Cyprus. There have been no unexpected types of adverse reactions reported to the company during this time and the device has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. Summary of Studies

A. Nonclinical Laboratory Studies

A number of publications are presented which address various chemical and biological properties of the Adatomed Silicone Oil OP5000.

1. Safety and Toxicity Studies.

Ocular toxicity of silicone oils has been related to the presence of unreacted low molecular weight components (LMWC's) and residual catalysts, both of which appear to affect ocular tissue in a dose dependent fashion (Gabel et al. 1987, Parel 1989, and Nakamura et al. 1991). The LMWC's include both linear and cyclic siloxanes, such as: hexamethyldisiloxane, octamethyltrisiloxane, decamethyltetrasiloxane, hexamethylcyclotrisiloxane (D_3), octamethylcyclotetrasiloxane (D_4), and decamethylcyclopentasiloxane (D_5). These impurities in the Adatomed Silicone Oil OP5000 are kept at very low levels through the control of several specifications: direct measurement of LMWC's; volatility (reflects the presence of small molecular weight components which can diffuse into adjacent tissues); resistivity (reportedly an index of ionic components of catalyst residues); and, measurement of reactive -OH end groups.

In a study of 14 differing silicone oil samples from various sources, Gabel (1987) found that the OP5000 product had the lowest level of low molecular weight components, volatile contaminants and ionic components compared with other samples of various silicone oils for intraocular use. Also, Nakamura et al. (1991) studied the gas chromatographic profiles of various silicone oil samples including the Adatomed Silicone Oil OP5000, concluding that the Adatomed product, like other medical grade oils, possessed fewer low molecular weight contaminants than commercial grade materials, such as those used in the manufacture of lubricants and transformer oils.

A series of investigators have examined the emulsification potential of silicone oils as related to their physical properties (Crisp et al. 1987; Gabel et al. 1987; Gabel 1989; Petersen and Rizau-Tondrow 1988; Mukai et al. 1972; and Ohira et al. 1988). In these studies the tendency for the oil to emulsify was attributed to factors which lower the interfacial tension of the oil, such as high levels of impurities left from processing, low viscosity, and low molecular weight contaminants. In contrast, Nakamura (1990) implicated the silicone oil fill volume of the vitreous chamber and concluded that higher viscosity products, such as the 5000 centistoke oil of OP5000, mechanically restrict oil droplet formation within the eye, thus reducing the

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possibility of emulsification of the oil.

In a study of the OP5000 oil in rabbits, Eckardt et al. (1990) noted the presence of a few epiretinal inflammatory cells and some silicone oil laden macrophages in the iris; he posited that, despite these findings in rabbits, the Adatomed Silicone Oil OP5000 was safe and should be recommended as a long term vitreous replacement in humans. A similar conclusion was reached by Hammer et al. (1988) who studied the OP5000 product in rabbit eyes. These authors recommended the more highly purified silicone oils as candidates for use in the human eye as a retinal tamponade for periods longer than 2 to 3 months.

Several cell culture studies of the Adatomed Silicone Oil OP5000 have been reported. In a study of bovine corneal endothelial cells, Hunold et al. (1989) found no significant changes in morphology or growth of the cells following incubations over 24 hours with the oil. Using Balb 3T3 cell cultures Parel (1989) also found no cytotoxic activity of a different 5000 centistoke oil. By examining cell spreading at an oil/aqueous interface, Sparrow et al. (1990) concluded that the Adatomed oil supported minimal growth and spreading of cells at the interface, suggesting that the content of polar impurities was low. Norman et al. (1990) studied the effects of silicone oils on corneal endothelial cell permeability and found that most oils examined, including the Adatomed Silicone Oil OP5000, caused passive increases in permeability to inulin or dextran. This finding is consistent with the known toxic effect of the silicone oils on corneal endothelial cells and does not preclude their use as long term tamponades in the posterior chamber.

In addition, there have been reports regarding the possibility that silicone oils, or the LMWC's, might be weak adjuvants under certain optimal conditions. The low concentrations of LMWC's present in this oil, the conditions of use, and the lack of reported cellular immune activity with silicone oil minimize the risk of adverse immunological effect from the use of this product. These potential minimal risks are adequately offset by the treatment benefits of the oil for this intended use.

Based on these studies, Adatomed Silicone Oil OP5000 has the appropriate physical and chemical properties for the stated indications for use and is considered safe for use in those indications.

2. **Sterilization.** Adatomed Silicone Oil OP5000 is supplied in single 10 mL or 15 mL sterile glass vials, sterilized by dry heat sterilization, capped with a stopper and housed inside sterilized peel back pouches intended for single use only. Adatomed Silicone Oil OP5000 contains no preservatives.

3. **Shelf Life Dating.** The shelf life testing results support a two-year shelf life for Adatomed Silicone Oil OP5000.

B. Clinical Studies

The data upon which the claims of safety and effectiveness for Adatomed Silicone Oil OP5000 are based were derived from the following studies: (1) one main investigation (Lucke and Laqua, 1990) of 299 subjects operated on by 3 co-investigating physicians at one site in

Germany from October 1984 through February 1989; (2) the sponsor's U.S. based multicenter prospective clinical trial involving 9 sites and 155 subjects; and, (3) independently sponsored investigations of the use of Adatomed Silicone Oil OP5000 in AIDS related CMV retinitis (205 eyes).

The findings from the last two studies do not conflict with the findings of the 299 patient study of Lucke and Laqua (Lucke study) nor do they present any unexpected results. The Lucke study may reflect slightly different outcomes or complication rates than the US population. This is likely due to case selection; other factors could be slightly different vitreous chamber fill techniques or individual operative techniques or practice referral patterns. Preoperatively, approximately 57% of all subjects entered into the Lucke study had more than one surgical procedure in an attempt to restore or improve vision. Some of the complications reported in the studies below may have been, in part, a result of previous ocular surgeries. The most relevant preoperative characteristic which influences the outcome is preoperative visual acuity. A review of these subjects confirms this to be the most common single parameter which influences study outcome. The fact that 33% of subjects in the Lucke study had preoperative ambulatory vision versus only 15% in the U.S. clinical trial may contribute to the slightly better outcomes, presented below, in the Lucke study.

1. **Demographics**

Lucke Study. The data upon which claims of safety and effectiveness are based were derived, for the most part, from the German study reported in K. Lucke and H. Laqua, *Silicone Oil in the Treatment of Complicated Retinal Detachments*, Springer-Verlag, Berlin, 161 pages, 1990. The database used in the publication of these results was provided to the applicant on diskette. Although the original database and publication reported on a total population of 483 eyes, a smaller subgroup of 299 eyes was isolated and analyzed from the database in which only the Adatomed Silicone Oil OP5000 product was used. In order to evaluate the longer term effects of the silicone oil, a subpopulation of 236 eyes having complete follow up at 6 months or longer was further analyzed and referred to as the "cohort group".

The objective of this study was to evaluate the acute and long-term ocular safety and effectiveness of Adatomed Silicone Oil OP5000 in the treatment of complicated retinal detachments due to proliferative vitreoretinopathy (PVR), proliferative diabetic retinopathy (PDR), traumatic perforating injury, giant tears, and posterior holes. This was an open-label, non-comparative study.

Following silicone oil instillation, examinations were conducted at the approximate intervals of 3, 6, 12, 18, 24, 36 and 48 months, or more frequently if required for management of complications due to the treatment or for management of the particular ocular pathology. The silicone oil was removed when, in the judgment of the investigator-surgeon, tamponade was no longer required.

The key measures of effectiveness were retinal reattachment and improvement in visual acuity. The key measures of safety were the time until development and incidence of complications such as keratopathy, increased intraocular pressure, or requirement to extract a cataractous lens, if present.

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In this study there were 299 subjects with indications for tamponade with silicone oil enrolled. Indications included 90 cases of PVR alone, 22 cases of perforating injury complicated with PVR, 2 giant tears complicated with PVR, 13 cases of posterior holes complicated with PVR, 3 cases of perforating injury and giant tear complicated with PVR, 112 cases of diabetic retinopathy, 9 cases of perforating injury alone, 16 cases of giant tears alone, 21 cases of posterior holes alone, and 11 other less common indications. Table 2 shows the baseline characteristics of the subjects in this study.

There were 186 males (62.2%) and 113 females (37.8%). The mean age was 45 years with a range of 3 to 84 years. Of the total 299 entered into the study, 215 were preoperatively phakic, 69 were aphakic and 15 were pseudophakic.

Table 2: BASELINE CHARACTERISTICS

	Lucke All Subjects (N=299)		Lucke Cohort (N=236)		US Clinical (N=155)		US AIDS (N=205)	
	N	%	N	%	N	%	N	%
Gender (Male/Female)	186/113	62%/38%	148/88	63%/37%	97/58	63%/37%	143/12	92%/8%
Mean Age (Yrs) and Range	45.0	(3-84)	44.7	(2-82)	48	0-88	40.2	23-89
Pre-Op lens status								
Phakic	215	72%	177	75%	53	34%	172	98%
Aphakic	69	23	50	21	50	32	1	0.5
Pseudophakic	15	5	9	4	52	34	3	1.7
Retina status								
Diabetic Retinopathy	133	44	93	39	21	14	12	5
Central Hole	34	11	28	12	4	3	3	1
PVR (all cases)	130	43	100	42	114	74	82	40
Previous surgery								
Prior detachment surgery	123	41	106	45	**			
Prior vitrectomy	53	18	44	19				

** *In all tables, areas where no data are presented represent cases in which the data are not available, because either the data were not reported for that study or the data were not broken-out in the applicable manner. See the narrative for additional explanations of the data.*

U.S. Clinical Trial. Additional relevant data from a U.S. based multicenter clinical trial from 9 sites support the findings of the Lucke study. The objective of this study was to determine the safety and effectiveness of silicone oil in the treatment of severe retinal detachments which have failed retinal reattachment by vitrectomy and intraocular gas. Results of this study were reported for the period August 1988 through August 1991. In this study of 155 subjects, 97 (62.6%) were male and 58 (37.4%) were female. The average age was 48.4 years with a range from less than 1 year to 88 years. Of the 155 subjects, 34% (53/155) were phakic at the beginning of the study;

14% (21/155) had PDR and 74% (114/155) had PVR. Age, sex and pre-existing conditions are shown in Table 2.

U.S. AIDS Study. In addition to the above multicenter investigational study, data were obtained from 14 independently sponsored IDE investigations of the Adatomed Silicone Oil OP5000 in order to evaluate the safety and effectiveness of this tamponade in the treatment of retinal detachments due to AIDS related CMV retinitis.

These studies of AIDS patients involved 205 eyes from 176 patients with CMV retinitis detachments treated with Adatomed Silicone Oil OP5000. Of the total, 92.3% of the subjects were male and the average age was 40.2 years.

2. Follow-up Time and Oil Removal

Lucke Study. Average time of follow-up was 17.3 months with a range of 1-49 months for all subjects and 21.4 months with a range of 6-49 months for the cohort analysis group. Silicone oil

Table 3: Length of Follow-up and Timing of Oil Removal

	Lucke All Subjects (N=299)		Lucke Cohort (N=236)		US Clinical (N=155)		US AIDS (N=205)	
	N	%	N	%	N	%	N	%
Follow-up (Months)								
Mean and Range	17 ± 13	1-49	21 ± 12	6-49	7.7 ± 6	1-26	3.95	0-34
> 1 month	299	100%	236	100%	142	92%		
> 3 months	257	86	236	100	100	65		
> 6	227	76	227	96	92	59		
> 12	176	59	176	74	39	25		
> 18	135	45	135	57				
> 24	85	28	85	36				
> 36	38	13	38	16				
Silicone Oil Removal								
Incidence of removal	94/299	31	92/236	39	41/155	27		
Time to removal (months)	13.9 ± 8.6		14.1 ± 8.5		4 ± 2.7			
Percent w/removal at:								
6 months		8						
12 months		24						

was removed in 31% of all subjects at an average of 13.9 months post instillation. In the cohort group oil was removed in 39% at an average of 14 months. Average time of follow-up and time to oil removal are shown in Table 3.

U.S. Clinical Trial. As of August 1991, of the 155 total subjects 106 subjects (68.4%) had been followed for at least 5-7 months or longer and 45 subjects (29%) had been followed for at least 12-14 months or longer. The average time in the study was 7.7 $\pm$ 5.8 months. Silicone oil was removed in 41/155 (26.5%) of all subjects in the study; the mean time to removal was 4 $\pm$ 2.7 months.

U.S. AIDS Study. The average last follow-up time where visual acuity status of the patient was determined was 3.95 months with a range from 0 to 35 months (N=194). While under normal circumstances this is a brief duration, it was further reported that 104 of the 176 subjects had died (59.1%) within a relatively short time from the date of surgery. Of the 49 cases where the date of death was known, it was calculated that the average time until death from the time of surgery was 6.4 months with a range of 0.6 months to 34 months.

3. **Effectiveness**

Lucke Study. The effectiveness of the silicone oil treatment is shown in Table 4. For all subjects attachment success at the final visit (mean 17 months for all subjects and 21 months for the cohort) was 74.6% (223/299). The retinal reattachment rate at the 6 month visit for the cohort group was 77.1% (182/236) and at the final visit the attachment rate was 75.4% (178/236). In this study there was no statistically significant difference between subjects with PDR and those with other indications (71.0% vs. 74.6% for all subjects and 70.5% vs. 75.4% at final visit in the cohort), while the attachment success from those with giant tears showed a more favorable trend than other indications: 93.7% (giant tears) vs. 74.6% (other indications) for all subjects and 92.3% (giant tears) vs. 75.4% (other indications) at final visit in the cohort. For all subjects and the cohort, respectively, there were 205/299 (68.5%) or 143/236 (60.6%) that did not have oil removed during the study. Of these, 68/205 (33.2%) or 51/143 (35.7%) progressed to a redetachment. In the all subject group, of the 94 eyes that had oil removed only 8 (8.5%) progressed to a redetachment; in the cohort, of the 93 eyes having oil removed, 7 (7.5%) redetachments were recorded. Those subjects with oil left in the eye were generally considered the more severe cases with a higher risk of redetachment following silicone oil removal.

In the all subjects group, 201/299 (67.2%) had preoperative visual acuities of count fingers or worse and 89/299 (29.7%) had visual acuities between 20/1000 and 20/125. In the cohort group, 159/236 (67.3%) had preoperative visual acuities of count fingers or worse and 72/236 (30.5%) had visual acuities between 20/1000 and 20/125. Only 9/299 (3.0%), all subjects, and 5/236 (2.1%), cohort, had acuities 20/100 or better. At the 6 month visit, 69% of subjects in the cohort showed an improvement in visual acuity over the preoperative value, 14.8% had no change and 15.3% worsened. In this cohort group at the final visit 66.5% showed improvement, there was no change in 13.6% and 19.9% worsened; the all subjects group showed a 70% improvement in vision at the final visit. In those instances where visual acuity was poor in spite of attachment of the retina the causes could be attributed to optic nerve atrophy, keratopathy, cataract, macular scars, and other unidentifiable causes.

As shown in Table 4, pre-operatively, only 33% of subjects had ambulatory vision (better than or equal to 20/1000); at the final visit, 68% (206/299) of all subjects and 72% (170/236) of the cohort had ambulatory vision. There was no statistical difference between all subjects and cohort subjects. Based upon survival analysis, 85% of all subjects and 88% of the subjects in the cohort group maintained ambulatory vision after one year.

There were no differences in outcome for visual acuity or reattachment rates based on age or sex.

U.S. Clinical Trial. Retinal attachment for all subjects at final visit (ranging from 1-26 months) was 63.9% (99/155) and macular attachment was 70.3% (109/155). In assessing the visual acuity of the 155 total subjects, there were 2 subjects missing preoperative data and there were 6 subjects missing postoperative data at the final visit. Preoperatively, only 15% (25/153) had ambulatory vision. Of the remaining 149 subjects at final visit, 67 (45.0%) showed improvement in visual acuity from the preoperative state, 38/149 (25.5%) had no change, and 44/149 (29.5%) had worsened vision. Of the total, 51 (34.2%) maintained ambulatory vision (20/1000 or better vision) at final visit.

Table 4: Effectiveness

	Lucke All Subjects (N=299)		Lucke Cohort (N=236)		US Clinical (N=155)		US AIDS (N=205)	
	N	%	N	%	N	%	N	%
Attachment Status								
Attached after 6 months	182/236	77%	182/236	77%				
Attached @ final visit	223/299	75	178/236	75	99/155	64	179/200	90
Having Ambulatory Vision								
Pre-op	98/299	33	77/236	33	25/153	15		
@ 6 months	188/236	80	188/236	80				
@ final visit	206/299	69	170/236	72	51/149	34		
Maintenance of ambulatory vision for 1 yr (by survival analysis, % of those having ambulatory vision)		85		88				
Improvement in vision @ final visit	165/299	70	157/236	67	67/149	45	82/183	45

U.S. AIDS Study. Subjects in this group were subject to vitrectomy followed by fluid/gas-gas/silicone exchange or direct fluid-silicone exchange with subsequent photocoagulation, cryopexy, or diathermy of retinal breaks or holes. Proliferative vitreoretinopathy was observed in 4.4% of the subjects. The retinal attachment rate at final visit was 89.5% (179/200) with macular attachment in 96.5% (194/201). Maintenance or improvement of visual acuity during the course of treatment occurred in 57.3% of eyes with some decline occurring by final visit (44.8%).

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4. **Safety**

Lucke Study. The incidence of cataract (shown in Table 5), as based upon development of post-discharge aphakia, was 47% (78/166) for all subjects and 56% (78/140) for the cohort. Excluded from this assessment are 133 eyes from the all subjects group and 96 eyes from the cohort group who were aphakic either pre-op or had the lens removed at the time of initial surgery. Within the first year, 42% (all subjects)-43% (cohort) of phakic subjects had cataracts removed, as calculated by survival analysis. This is consistent with development of cataract in subjects undergoing vitrectomy without the use of silicone oil.

Table 5: Safety

	Lucke All Subjects (N=299)		Lucke Cohort (N=236)		US Clinical (N=155)		US AIDS (N=205)	
	N	%	N	%	N	%	N	%
CATARACT	78/166	47%	78/140	56%	10/14	71%	63/188	34%
Removed w/in 1 year		42		43		45		
ANTERIOR CHAMBER OIL MIGRATION	50/299	17	47/236	20			3/176	1.7
Keratopathy	15/50	30	14/47	30				
Glaucoma	15/50	30	15/47	32				
KERATOPATHY								
Combined	22/293	8	20/231	9	13/149	8.7	1/176	0.6
Phakic	9/212	5	9/174	5				
Aphakic	12/66	18	10/48	21				
Pseudophakic	1/15	7	1/9	11				
GLAUCOMA								
Combined	57/283	20	44/226	19	12/125	9.6	1/176	0.6
Phakic	47/205	23	36/170	21				
Aphakic	9/65	14	7/47	15				
Pseudophakic	1/13	8	1/9	11				
Attached retina pre-op	10/12	83	8/10	80				
Oil removed prior to glaucoma	3/57		3/44					
HYPOTONY	13/296	4	13/234	6				

In 17% (50/299) of all subjects and 20% (47/236) of the cohort group, oil emulsification and/or migration into the anterior chamber was observed. Migration into the anterior chamber occurred in both phakic and aphakic subjects. Keratopathy was noted to occur in 30% of all subjects that had silicone oil emulsification or migration into the anterior chamber. Glaucoma developed in approximately 30% of all subjects that had migration of the oil into the anterior chamber, or silicone oil emulsification.

The incidence of new cases of keratopathy (excluding preoperative cases) was 7.5% (22/293) in the all subject group (6 preexisting) and 8.6% (20/231) in the cohort group (5 preexisting). The keratopathy rate was higher in preoperative aphakic subjects (18% in all subjects and 21% in the cohort) than in either phakic subjects (4% in all subjects and 5% in the cohort) or pseudophakic subjects (7% in all subjects, 11% in the cohort).

The incidence of new cases of persistent glaucoma with intraocular pressure (IOP) greater than 23 mm Hg (excluding 16 cases of preoperative glaucoma) in all subjects was determined to be 20.1% (57/283). Of these 57 cases, 81% (46/57) had attached retinas. The rate calculated from the cohort (excluding 10 cases of preoperative glaucoma) was 19.5% (44/226) of which 84% (37/44) had attached retinas. By survival analysis, higher rates of glaucoma were observed in subjects with preoperative indications of PDR and posterior holes: 23% (21/91) of subjects in the cohort group with pre-operative PDR developed glaucoma and 23% (6/26) of the subjects with preoperative posterior holes developed glaucoma. Out of the 57 total subjects in the all subjects group developing glaucoma, only 3 had the oil extracted prior to its onset.

New instances of hypotony were observed in 13/296 (4%) of subjects (3 subjects had pre-existing hypotony); this hypotony occurred with a rapid onset of within 6 months. There was no difference between the all subjects group and the cohort group.

In addition to the complications above, other less common adverse findings included redetachment (14% of all subjects), optic nerve atrophy (11% of all subjects), and rubeosis iridis (10.4% of all subjects). Other complications occurring at a rate greater than 2% were temporary IOP increase, macular pucker, vitreous hemorrhage, phthisis, traction detachment, and angle block. The following complications occurred at rates of less than 2%: subretinal strands, retinal rupture, endophthalmitis, subretinal silicone oil, choroidal detachment, aniridia, PVR reproliferation, cystoid macular edema, and enucleation. None of these complications were unexpected in context of the preoperative indications of these subjects and the surgical exigencies. Diabetic subjects represented most of the cases of rubeosis iridis. Prior to entry into the study, approximately 57% of all subjects had more than one surgical procedure to attempt to restore or improve vision.

U.S. Clinical Trial. Of the 53 phakic subjects entered into the study, 24 (45.3%) required removal of the lens. Of the 29 subjects that were still phakic at their final visit, 14 had clear lens preoperatively; of these 14 eyes, 10 (71.4%) were clearly noted to have developed cataracts. Also, in the 52 pseudophakic subjects, 12 (23.1) had their intraocular lens (IOL) removed. The rate of de novo keratopathy was 8.7% (13/149). The total incidence rate of post operative glaucoma at final visit was 12/125 (9.6%). Of the remaining 30 subjects, 9 had glaucoma preoperatively, 19 were missing preoperative data on IOP and 2 were missing any postoperative data.

U.S. AIDS Study. In this population 98% of eyes were phakic. Cataract development occurred in 33.5% (63/188) within approximately 4.6 months of oil instillation. There was one instance of keratopathy and one instance of glaucoma reported.

Age and Gender Analysis. Age and gender analysis was performed using the Lucke cohort group of 236 eyes. There were no statistically significant differences for gender, age, or the interaction of gender and age for anterior chamber oil migration, keratopathy, and glaucoma. For all of the observed adverse events, only two showed any trend regarding age or gender: 1) for optic nerve atrophy there was a statistically significant difference for age, in that the incidence in subjects less than 50 years old was 15.3% (22/144), while the incidence in subjects over 50 years of age was 7.6% (7/92); 2) for rubeosis iridis, although the overall effects of age and gender were not significant, there was a statistically significant difference in the interaction term, such that the incidence for males over 50 years old was 20.5% (9/44), while the incidence in females over 50 years of age was 2.1% (1/48). Because of the small sample size and the numerous and diverse complications with which these subjects presented, no definitive conclusions can be stated based on these findings. Of note here is the fact that the rate of postoperative glaucoma was unaffected by age, gender, or the interaction of age and gender.

IX. Conclusion Drawn From the Studies

A. Discussion of Valid Scientific Evidence

In accordance with 21 CFR §860.7 the validity of the evidence presented in this Premarket Approval (PMA) application was based upon an objective trial without a matched control. The clinical investigators were vitreoretinal surgeons with long standing experience in the standard methodologies for retinal reattachment procedures. Comparative study designs were considered, but rejected due to ethical considerations and the severe nature of the retinal disease in these study subjects. Over 40% of the study subjects had previous reattachment surgeries which had failed.

The evidence supporting the reasonable assurance of safety and effectiveness from the literature-based analysis of clinical studies conducted with the Adatomed Silicone Oil OP5000 was:

	Lucke Study Cohort		Lucke All Subjects		US Clinical Trial
Total number of eyes treated with OP5000	236		299		155
Average follow up (months)	21.4		17.3		7.7
	1 year[1]	Final visit	1 year	Final visit	Final visit
Retinal attachment rate	67%	75%	65%	75%	64%
Ambulatory Vision[2]	88%	72%	85%	69%	34%
Cataract development in phakic subjects	43%	56%	42%	47%	71%
Keratopathy	7%	9%	7%	8%	9%
Glaucoma	17%	19%	20%	20%	10%

B. Benefits of Silicone Oil Tamponade

1. **Duration of tamponade.** When compared with other available products, silicone oil provided long-lasting tamponade, well beyond 1 month period of time and as long as 1-2 years without repeated intraocular injections. The half-lives of intraocular air and SF_6 bubbles are 2 and 4 days, respectively, and the longest half-life with other gases is 20 days (C_3F_8).

2. **Optical properties.** Adatomed Silicone Oil OP5000 is optically clear. This property allows for good vision through the bubble as early as in the immediate post-operative period, particularly in aphakic patients. Because the oil forms a convex surface near the pupil, the hyperopia experienced by aphakic patients is corrected and the eye becomes myopic (to about +5

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1 *By survival analysis.*

2 *The incidence of ambulatory vision pre-operatively was 33% in both the Cohort and All subjects groups and 15% in the US Clinical Trial group.*

diopters residual refraction).

3. **Mobility of the patient.** Changes in the external atmospheric pressure have no influence on the properties of silicone oil that has been instilled into the eye. Therefore, airline travel is not precluded for patients who receive silicone oil, in contrast to patients receiving a gas tamponade. These properties and the optical properties of the silicone oil mean that ambulatory visual acuity usually returns earlier in the course of recovery, usually immediately postoperatively, than with intraocular gas tamponade, which usually requires removal of the gas prior to recovery of ambulatory visual acuity.

C. Risks of Silicone Oil Tamponade

1. **General health.** There have been no reports of intraocular Adatomed Silicone Oil OP5000 causing any adverse event as related to the general health of the patient. The PMA contained a literature search of all silicone oil publications as related to retinal detachment surgery in humans. There were no references to any systemic problems and no mention of oil migration outside of the orbit.

2. **Ocular complications.** Treatment with intravitreal Adatomed Silicone Oil OP5000 resulted in several known and expected ocular complications. These included cataract in phakic patients (at least 50% of subjects within 18 months), keratopathy (20%), and glaucoma (20%). Each of these complications can be treated either with devices, surgically, or with medication: cataract by lens removal and intraocular lens placement; keratopathy by chelator treatment or corneal graft surgery; and, glaucoma by anti-glaucoma drugs or filtration surgery. Therefore, although posing a threat for eventual loss of visual acuity, these complications can be treated and are of relatively lower risk in view of action of silicone oil to decrease the incidence of complete and rapid loss of vision due to retinal detachment.

D. Conclusion

In conclusion, the relative benefit/risk ratio for Adatomed Silicone Oil OP5000 was weighed based on the following:

1. an acceptable chance for restoration or maintenance of ambulatory vision;

2. advantage over the use of gases in effective duration of tamponade for patients with these complicated detachments in that, for long-term tamponade, the silicone oil will remain until the oil is removed; and,

3. availability of treatment for many of the ocular complications resulting from the use of the silicone oil.

X. **Panel Recommendations.** At an advisory meeting on October 28-29, 1993, the Ophthalmic Devices Panel recommended that Chiron Vision Corporation's PMA for Adatomed Silicone Oil OP5000 be approved. The panel offered no specific conditions to approval; however, they discussed the importance of appropriate labeling for use where other interventions failed or were not appropriate for patient management.

XI. **CDRH Decision.** CDRH has determined that, based on the data submitted in the PMA, there is reasonable assurance that Adatomed Silicone Oil OP5000 is safe and effective for its intended use, and issued an approval order on November 4, 1994.

XII. **Approval Specifications.** The applicant's manufacturing facility was inspected on May 4, May 5, and May 11, 1994, and was found to be in compliance with the device Good Manufacturing Practice regulation.

In addition to the "Conditions of Approval" enclosed with the approval letter, Chiron Vision Corporation must submit within 60 days a draft protocol for a postapproval prospective study. This protocol should provide data on 100 subjects that document the timing of silicone oil removal and that assess complication rates in relation to removal times. Anatomic reattachment and visual acuity outcomes should be the end points studied in relationship to the timing of oil removal.

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Adatomed Silicone Oil OP5000
(Sterile purified polydimethylsiloxane, 5000 centistokes)

DESCRIPTION

Adatomed Silicone Oil OP5000 is a sterile, highly purified long chain polydimethylsiloxane of the formula $(CH_3)_3SiO\text{-}[(CH_3)_2SiO]_n\text{-}Si(CH_3)_3$. It is a clear colorless liquid at room temperature with a viscosity of 5000-5400 centistokes (nominal 5000 centistokes). It has a specific gravity (25°C) between 0.96 and 0.98 g/cm3 and a refractive index (25°C) between 1.403 and 1.405. Each 1 ml contains solely polydimethylsiloxane oil in neat form.

INDICATIONS FOR USE

Adatomed Silicone Oil OP5000 is indicated for use as a prolonged retinal tamponade in selected cases of complicated retinal detachments where other interventions are not appropriate for patient management. Complicated retinal detachments or recurrent retinal detachments occur most commonly in eyes with proliferative vitreoretinopathy (PVR), proliferative diabetic retinopathy (PDR), cytomegalovirus (CMV) retinitis, giant tears, and following perforating injuries. **Adatomed Silicone Oil OP5000** is also indicated for primary use in detachments due to Acquired Immune Deficiency Syndrome (AIDS) related CMV retinitis and other viral infections.

CONTRAINDICATIONS

As silicone oil can chemically interact and opacify silicone elastomers, the use of **Adatomed Silicone Oil OP5000** is contraindicated in pseudophakic patients with silicone intraocular lenses (IOLs).

PRECAUTIONS

- **Adatomed Silicone Oil OP5000** is supplied in a sterile vial intended for single use only and contains no preservative.
- Do not resterilize.
- Discard unused portions of **Adatomed Silicone Oil OP5000.**
- Do not admix oil with any other substances prior to injection.
- Product should be discarded following expiration date.
- The safety and effectiveness of long-term use of **Adatomed Silicone Oil OP5000** has not been established.

ADVERSE REACTIONS

The data supporting the rates of occurrence of adverse reactions were derived from the following studies: (1) a study reported in K. Lucke and H. Laqua, *Silicone Oil in the Treatment of Complicated Retinal Detachments*, Springer-Verlag, Berlin, 161 pages, 1990, (299 eyes with Adatomed Silicone Oil OP5000; 236 with complete follow up at 6 months or longer); (2) a U.S. based multicenter clinical trial (155 patients); and, (3) independently sponsored investigations of the use of the oil in AIDS related CMV retinitis (205 eyes). The percentages reported below represent the range of occurrence for all of the studies reporting the same adverse reaction. In

cases where only one of the studies recorded a particular endpoint, only that percentage, as well as the study from which it was derived, is reported.

Cataract. Approximately 50-70% of phakic patients developed a cataract within 12 months of oil instillation. Approximately 33% of phakic AIDS CMV retinitis patients developed some degree of cataract within an average 4-5 month time frame from oil instillation.

Anterior chamber oil migration. In 17-20% of treated patients oil emulsification and/or migration into the anterior chamber was observed. Migration into the anterior chamber occurred in both phakic and aphakic patients.

Keratopathy. From 8%-20% of patients developed keratopathy (0.6%, AIDS study). This complication occurred most frequently in aphakic patients (18-21%) and in the patients in whom oil had migrated into the anterior chamber (30%, Lucke study); the keratopathy in these cases was attributed to prolonged physical contact between the corneal endothelium and the silicone oil.

Glaucoma. Approximately 19-20% (0.6%, AIDS study) of patients developed a persistent elevation in intraocular pressure (> 23-25 mm Hg, depending on study definitions). The neovascular glaucoma rate was about 8% (Lucke). Moderate temporary post-operative increases occurred within the first 3 weeks of treatment. Thereafter, secondary ocular hypertension occurred by several mechanisms. Glaucoma complications occurred in approximately 30% of patients in which anterior chamber oil was noted (Lucke study). Patients with proliferative diabetic retinopathy were at highest risk for development of glaucoma following silicone oil instillation into the vitreous space.

Other. In addition to the complications above, other less commonly occurring reactions reported in Lucke (236 eyes), in greater than 2% of patients, ranked by frequency of occurrence included:

Adverse Event

Redetachment
Optic nerve atrophy
Rubeosis iridis
Temporary IOP increase
Macular pucker
Vitreous hemorrhage
Phthisis
Traction detachment
Angle block

The following complications occurred at rates of less than 2%: subretinal strands, retinal rupture, endophthalmitis, subretinal silicone oil, choroidal detachment, aniridia, PVR reproliferation, cystoid macular edema, and enucleation.

DOSAGE AND ADMINISTRATION

Adatomed Silicone Oil OP5000 can be used in conjunction with or following standard retinal surgical procedures including scleral buckle surgery, vitrectomy, membrane peeling, and retinotomy or relaxing retinectomy.

Aseptically remove the sterile vial of **Adatomed Silicone Oil OP5000** from the peel back pouch onto the sterile tray. Load the oil into a sterile Luer-Lok screw syringe or Luer-Lok syringe adaptable to an automated pump system. Introduction of air bubbles into the oil should be avoided by careful withdrawal or decanting of the oil into the syringe. The oil can be injected into the vitreous from the syringe via a single use cannulated infusion line or syringe needle. Subretinal fluid can be drained with a flute needle concurrent with **Adatomed Silicone Oil OP5000** infusion. The vitreous space can be filled with the oil to between 80% and 100% while exchanging for fluid or air, taking necessary precautions to avoid high intraocular pressure from developing during the exchange. Because the **Adatomed Silicone Oil OP5000** is less dense than the eye's aqueous fluid, a basal iridectomy at the 6 o'clock meridian (Ando iridectomy) is recommended to minimize oil induced pupillary block and early angle-closure glaucoma. Upon choice of the physician, it may be desirable to have the patient assume a face-down posture during the first 24 hours following surgery.

The patient should be monitored closely by the physician for development of glaucoma, cataract, and keratopathy complications and be scheduled for follow up reexamination at regular intervals.

It is recommended that **Adatomed Silicone Oil OP5000** be removed at an appropriate interval within 1 year following instillation if the retina is stable, attached, and without significant remnants of proliferation. Although there is insufficient clinical evidence to support justification for longer term tamponade, whether or not the oil should be removed in patients at high risk for redetachment or the development of phthisis and shrinkage due to hypotony must be determined individually by the physician. In order to minimize the number of invasive traumatic experiences for patients with AIDS and CMV retinitis at high risk for redetachment and who have a shortened expected lifespan, it may be desirable to avoid silicone oil removal procedures if the patient concurs.

Adatomed Silicone Oil OP5000 can be removed from the posterior chamber by withdrawal with a normal 10 mL syringe and a wide bore 1 mm cannula. By repeated oil-fluid exchange most of the remaining small silicone oil droplets can subsequently be mobilized and removed from the eye. Alternatively, oil may be passively removed by infusion of an appropriate aqueous solution under the oil bubble, while allowing the oil to effuse out of a sclerotomy incision, or a limbal incision in aphakic patients.

As there is a possible correlation between the migration of Adatomed Silicone Oil OP5000 into the anterior chamber and the appearance of corneal changes such as edema, hazing or opacification, Descemet folds, or decompensation, regular monitoring of the patient's corneal status should be performed and early corrective action taken if necessary, including extraction of the oil from the anterior chamber. Large bubbles or droplets of oil in the anterior chamber can be removed manually by syringe. Further standard practice for medical treatment of the keratopathy is recommended.

Temporary pressure increases more than 3 weeks after surgery which can normalize either spontaneously or which can be corrected by surgical treatment are those in which the **Adatomed**

Silicone Oil OP5000 causes a mechanical blockage of the pupil or inferior iridectomy or causes chamber angle closure by forcing its way anteriorly. In these situations some of the oil may be withdrawn to relieve the mechanical force of the oil interface. Presence of **Adatomed Silicone Oil OP5000** droplets in the anterior chamber may also cause a chronic outflow obstruction of the trabecular meshwork. In such situations elevated intraocular pressure can be managed with anti-glaucoma medication in the majority of outflow obstruction patients.

CLINICAL EXPERIENCE

The clinical experience data were derived from data in K. Lucke and H. Laqua, from a U.S. based multicenter clinical trial, and from independently sponsored investigations of the use of the oil in AIDS related CMV retinitis. Although the original database for the Lucke study reported on a total population of 483 eyes, a smaller subgroup of 299 eyes was isolated and analyzed from the database in which only the **Adatomed Silicone Oil OP5000** product was used. A subpopulation of 236 eyes having complete follow up at 6 months or longer was further analyzed.

The objective of the Lucke study was to evaluate the long-term ocular safety and efficacy of **Adatomed Silicone Oil OP5000** in the treatment of complicated retinal detachments due to PVR, PDR, traumatic perforating injury, giant tears, and posterior holes. This was an open-label, non-comparative study. Examinations were conducted at the approximate intervals of 3, 6, 12, 18, 24, 36 and 48 months, or more frequently as required. The silicone oil was removed when, in the judgment of the investigator-surgeon, tamponade was no longer required. The key measures of efficacy were retinal reattachment and improvement in visual acuity.

The percentages shown below represent the range of occurrence for all of the studies; in cases where only one of the studies recorded a particular endpoint, only that percentage, as well as the study from which it was derived, is reported.

ANATOMIC REATTACHMENT RATES.

Successful reattachment of the retina occurred in 64-75% of the patients who were treated with **Adatomed Silicone Oil OP5000.** This rate varied depending on the specific etiology of the disease and the severity of the condition. In AIDS CMV retinitis patients receiving silicone oil as a primary means for reattaching the retina, attachment rates were as high as 90% within an average 6 month follow up period.

VISUAL ACUITY OUTCOMES.

From 45-70% of patients showed improvements in visual acuity at six months. In about 15-26% of patients visual acuity did not change and in about 15-30% worsening of visual acuity occurred. Deterioration of visual acuity in treated patients appeared to be related to redetachment of the retina, further progression of retinal disease, or to keratopathy and cataract complications. In AIDS CMV retinitis patients improvement or maintenance of visual acuity was documented in 57% of the patients within an average 6 month follow up period. In AIDS patients, further decline in visual acuity was seen due to continuing progression of retinal and optic nerve disease and development of oil related cataracts in 33% of patients within 4-5 months of oil instillation.

HOW SUPPLIED

Adatomed Silicone Oil OP5000 is supplied in single 10 mL or 15 mL sterile glass vials capped with a septum and housed inside sterilized peel back pouches. Each single dose unit pouch is contained inside an overwrapped carton. Also, packs of 10 single dose units are available.

STORAGE

Store at room or cool temperature (8° to 24°C)

Adatomed Silicone Oil OP5000 is manufactured by Adatomed GmbH, Munich, FRG, a majority owned division of Chiron Vision Corporation, Inc, Irvine, CA.

Distributed by Escalon Ophthalmics, Inc., Montgomery Knoll, 182 Tamarack Circle, Skillman, NJ 08558., Telephone 800-468-4848.

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